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EXAMINER	
CHEN, STACY BROWN	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 05/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,188	JORDAN ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/16/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-46 and 48* is/are pending in the application.

4a) Of the above claim(s) *21-46 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-20* is/are rejected.

7)☒ Claim(s) *14 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed March 16, 2006 is acknowledged and entered. Claims 21-46 and 48 are pending and withdrawn from consideration as being drawn to non-elected inventions. Claims 1 and 3-20 are pending and under examination.

2. The following objection and rejections are withdrawn or moot:

- The objection to claims 1 and 5 for reciting acronyms without spelling them out at their first occurrence in the claims, is withdrawn in view of Applicant's amendment.
- The rejection of claims 14 and 15 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of the statement filed December 21, 2005 in support of biological deposits DSM ACC2444 and DSM ACC2445, mAb IE273 and mAb IE245, respectively.
- The rejection of claim 47 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is moot in view of the cancellation of claim 47.
- The rejection of claim 47 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is moot in view of the cancellation of claim 47.
- The rejection of claims 1-20 and 47 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is moot with respect

to cancelled claims 2 and 47. The rejection is withdrawn with regard to claims 1, 3-7 and 12-20, in view of Applicant's amendments.

Claim Rejections - 35 USC § 112

3. The rejection of claims 8-11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained for reasons of record. Claim 8 and dependent claims 9-11 recite, "zyxin derivative". The metes and bounds of the identity of zyxin derivatives are not discernable. It is unclear how altered the derivatives are in comparison to the original proteins, or what portions of the original protein are retained in the derivatives. The specification does not offer any further guidance on these terms. Applicant points to [026] of the specification, however, a review of this paragraph does not offer any definition of the term, "zyxin derivative". It is suggested that derivative language be removed in order to overcome this rejection.

4. (*New Rejection*) Claims 5-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims recite, "VASP fragment" and "zyxin fragment", respectively. The specification does not support these terms, although Applicant considers the term "fragment" to be an alternative to "derivative". Since the meaning of the term "derivative" was questioned in

the 112, second paragraph rejection, the term, "fragment" cannot be considered an alternative that encompasses the same scope. A derivative of VASP may imply that modifications have occurred throughout VASP, while a fragment of VASP implies that a piece of VASP is selected. These two meanings do not encompass the same scope, therefore, the term "fragment" is not supported in the specification.

5. (*New Rejection*) Claims 5-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to processes for identifying chemical compound(s) that modulate an interaction between an EVH1 (**E**na-**V**ASP (*Drosophila melanogaster enabled*-vasodilator-stimulated phosphoprotein) **H**omology **1**) binding domain and an EVH1 domain. In some claimed embodiments, the EVH1 domain is a VASP fragment. In other embodiments, the EVH1 binding domain is a zyxin fragment. The large genus of VASP fragments and zyxin fragments is not adequately described in the specification such that one of skill in that art would be put in possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor provided in the

specification is a partial structure in form of "fragment". The fragments are not required to have any particular function, nor are there any methods of making the fragments that are functional. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived.

Claim Rejections - 35 USC § 103

6. Claims 1, 3-10, 12, 13 and 16-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gertler *et al.* (WO 98/01755, "Gertler"), in view of Reinhard *et al.* (*PNAS*

USA, 92:7956-7960, 1995, "Reinhard") and Evangelista *et al.* (US 5,262,299, "Evangelista"). (The rejection of claim 2 is moot in view of the cancellation of claim 2.)

The rejection is repeated here for convenience:

The claims are drawn to a process for identifying a chemical compound which modulates an interaction between an EVH1 binding domain (or a protein having said domain) and an EVH1 domain (or a protein having said binding domain). The process comprises the steps of bringing the two proteins in contact in the presence of the candidate compound, incubating the mixture with a primary and secondary labeled antibody that binds to either of the two proteins. Detection of the labeled antibody indicates that the antibody bound said EVH1 domain protein. The process takes place on a solid body, such as a microtiter plate coated with the EVH1 binding domain protein. In particular embodiments, the protein having the EVH1 domain is VASP of a vertebrate, specifically human VASP. The protein having the EVH1 binding domain is zyxin, specifically human zyxin. VASP binds zyxin. Also claimed are polyclonal and monoclonal antibodies in the incubation step of the process. In another embodiment, the antibody label is a radioactive isotope, a fluorescent dye or an enzyme, such as alkaline phosphatase, beta-galactosidase, lanthanide in a europium complex.

Gertler discloses a screening method for a modulator of a protein (*Mammalian Ena*, abbreviated "*Mena*") having an EVH1 binding domain that binds to EVH1 proteins such as zyxin and vinculin (abstract). In one embodiment, the modulator is a chemical compound (page 28, lines 28-32). Assays are disclosed suitable for high throughput screening assays designed to identify modulators of *Mena* or Ena-VASP-like (abbreviated *Evl*) expression and/or activity (page 23). In one embodiment, the protein is contacted with a binding partner in the presence of

the candidate modulating compound. The protein and its binding pair will either complex or remain separate proteins. If a complex forms, the candidate has no modulation activity on the EVH1 protein or binding domain. If a complex does not form, then the candidate has modulation activity on the EVH1 protein and binding protein (page 23, lines 13 through page 24, line 19). Gertler discloses that secondary antibodies may be used to detect anti-EVH1 antibodies. The assays are conducted on solid phase (page 24, lines 24-29). Also disclosed are monoclonal and polyclonal antibodies that bind to proteins comprising EVH1 domains (page 17, lines 16-30). Further, the EVH1 domain protein is a fusion protein with glutathione S-transferase (page 24, lines 24-27). Gertler suggests the use of a solid phase for the assay, however, there is no teaching about a microtiter plate as claimed by Applicant. Gertler suggests the use of labels for the antibodies, however, there is no teaching regarding the types of labels. Specifically, Gertler is silent on alkaline phosphatase or beta-galactosidase, and lanthanide in a europium complex.

However, Reinhard discloses as assay wherein a zyxin family member (p83) was coated to the surface of microtiter wells and human VASP was applied as a ligand (page 7956, column 2, first full paragraph, and page 7958, second column, first paragraph). Reinhard mentions that a human zyxin homologue was discovered (page 7959, first column, first full paragraph). Reinhard also discloses a double-label immunofluoresence assay monoclonal and polyclonal antibodies labeled with rhodamine and FITC (page 7958, second column, third full paragraph, and Figure 4 caption). Further, Evangelista discloses various labels used for detection assays. The labels include lanthanide chelate (europium complex), alkaline phosphatase and beta-galactosidase (Figures 1-13).

It would have been obvious to incorporate the teachings of Reinhard and Evangelista into the method of Gertler. One would have been motivated to perform the detection assay on a solid support, such as a microtiter plate, in order to test more candidate compounds. One would have had a reasonable expectation of success because Gertler suggest the use of a solid body, and Reinhard performs a similar assay to Applicant's assay with VASP and a zyxin family member. One would have been motivated to use the labels taught by Evangelista because Gertler suggests the use of labels for the antibodies. One would have been motivated to use Evangelista's label because Evangelista teaches that the lanthanide label is highly sensitive. As for beta-galactosidase and alkaline phosphate labels, these are common labels in the art of immunoassay, evidenced by Evangelista's Figures detailing several of the well-known labels in the art. Regarding the limitation of claim 13, wherein the monoclonal antibody is synthesized using hybridoma cells, Gertler's monoclonal antibodies anticipate this limitation. Monoclonal antibodies are only ever produced from hybridoma cells to date. Regarding the use of human VASP and zyxin in the immunoassay, one would have been motivated to use human proteins in order to discover chemical compounds appropriate for human administration should any be found effective and safe. Therefore, the invention as a whole would have been *prima facie* obvious at the time of the invention.

7. Applicant's arguments have been carefully considered but fail to persuade. Applicant's arguments are primarily directed to the following:

- Applicant argues that the Office has mischaracterized the teachings of Gertler. Specifically, Applicant asserts that page 23 of the Gertler teaches purification of

proteins, such as making antibodies thereagainst, making modified peptides, such as synthetic, recombinant or fusion proteins, and mutated proteins.

- In response to Applicant's arguments, Gertler discloses a screening method for a modulator of a protein (*Mammalian Ena*, abbreviated "*Mena*") having an EVH1 binding domain that binds to EVH1 proteins such as zyxin and vinculin (abstract). In one embodiment, the modulator is a chemical compound (page 28, lines 28-32). Page 8, lines 26-38, claim 1, disclose methods suitable for high throughput screening assays designed to identify modulators of *Mena* or Ena-VASP-like (abbreviated *Evl*) expression and/or activity (see page 28, lines 28-32 and also page 23).

- Applicant argues that the teachings of Gertler, page 28, lines 28-32, have also been mischaracterized. Applicant asserts that rather than testing unknown compositions for modulatory action, Gertler teaches methods of assaying for expression, such as protein synthesis of Men or Evl or quantifying activity of proteins expressed. Binding partners such as zyxin are suggested as controls in these assays. Applicant argues that the teachings of Gertler at page 24, lines 24-29, are in reference to mutant proteins, and should not be stretched into a grander picture. Applicant argues that the mutant is suggested as a tool to screen for agonists that replace or enhance *Mena*-profilin binding. Applicant asserts that the substitute compounds such as recombinant or chimeric proteins might be tested for binding ability.

- In response to Applicant's arguments, Gertler discloses that screening methods, such as high throughput screening assays, are useful to identify modulators of *Mena* or *Evl* expression or activity (page 28, lines 21-28).

- Applicant argues that a solid phase detection system is taught in Gertler (page 25, lines 29-31) where solid phase purification is taught; and page 25, line 27, where Western blotting is mentioned as a tool in an assay for *Mena* or *Evl* expression.
  - In response to Applicant's arguments, Gertler teaches kits and multicontainer units comprising reagents and components for practicing the disclosed assays (page 29, lines 16-38).
- Applicant argues that while Gertler would appear to teach purification and detection methods to the skilled artisan, one cannot say that these teachings teach all the limitation of the instantly claimed invention. Applicant argues that the combination of references fails to teach or suggest all elements necessary to reject the claims.
  - In response to Applicant's arguments against the Gertler reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).
  - In response to Applicant's argument that Gertler in combination with the other references fail to teach the claimed invention, Applicant has failed to demonstrate that the teachings of Gertler encompass the claimed invention (in view of the arguments presented above) in combination with the other references. Gertler

discloses all the elements asserted by the Office, therefore, the combination of references is proper and teaches all the elements of the claims.

Conclusion

8. No claim is allowed. Claims 14 and 15 are objected to for depending from rejected claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 5/24/06
Stacy B. Chen
Primary Examiner
May 24, 2006